Clinical staging model in offspring of parents with bipolar disorder

Clinical Staging Model in Offspring of Parents with Bipolar Disorder: A Systematic Review

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Abstract

Objective: We sought to systematically review the literature on the psychiatric risk of offspring of parents with bipolar disorder (OPBD) using a developmental psychopathology framework. The review also sought to establish the utility of clinical stage modelling as a framework for identifying precursor disorders to later onset of bipolar disorder (BD) in OPBDs.

Methods: A systematic search was performed using EMBASE, PsychINFO and Medline. Reference lists of included studies and previous reviews were also searched. Studies were included if they reported diagnostic outcomes for children, adolescents and young adult offspring of parents diagnosed with BD.

Results: Twenty-six studies were identified representing 21 individual cohorts. The review identified that OBPD present as a high-risk group for a range of mood and non-mood disorders in childhood, adolescence and young adulthood. The trajectory of risk was from non-mood disorders in childhood via mood disorders in early adolescence towards mania/hypomania in late adolescence and early adulthood. From a clinical staging perspective, childhood anxiety disorders were associated with later onset of BD. Recurrent substance use disorder was identified as a risk in OPBD during late adolescence and early adulthood. Quality ratings indicated studies were methodologically robust.

Conclusions: Our review provides evidence for a developmental psychopathology trajectory of precursor risks to BD in OPBD. There is support for clinical stage modelling as a conceptual framework for understanding developmental risk in OPBD and as a tool for developing early and individualized intervention strategies.

Key Words: Bipolar disorder, high-risk offspring, developmental risk, clinical staging model

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Introduction

Bipolar disorder (BD) is a chronic mood disorder characterised by episodes of mania or hypomania alternating with depression, with significant comorbidity, suicide risk, interpersonal, societal and economic costs (1-6). Retrospective reports suggest that the majority of individuals experience the first symptoms of BD prior to adulthood (7), with a mean age of onset estimated to be between late adolescence and early adulthood (8). More than half of BD patients report either under-diagnosis or misdiagnosis prior to index diagnosis of BD, with duration of untreated illness of up to 10 years (9,10). Improving the understanding of early, prodromal stages of BD through the delineation of high-risk sub-groups (as in non-affective psychosis; 11) has implications for improving the precision of BD diagnosis, expanding early intervention strategies and generating primary prevention strategies (12,13).

Risk of Psychopathology in OPBD

One approach to identification of early stage BD is through assessment of developmental pathways of cohorts at high-risk for developing BD – or offspring of parents with bipolar disorder (OPBD). Evidence from family, twin, and adoption studies suggest a heritability rate of up to 85% in monozygotic twins (14) and a 5-to-10-fold higher prevalence of BD amongst first-degree relatives compared to the general population (15). Population cohort data suggests that offspring of two BD-diagnosed parents have a 5.7-fold higher risk of developing BD compared to offspring with only one bipolar parent, and a 51.9-fold risk compared to offspring with no bipolar parents (16). The significantly elevated risk of BD in OPBD raises the question of whether, within this risk trajectory, there are both distinct “ultra-high risk endophenotypes” and whether OBPD who go on to develop BD progress through recognizable clinical stages en-route to a later diagnosis (17).

It is also increasingly apparent, that in addition to elevated risk of later BD, OBPD present with an elevated risk of a broad spectrum of mood and non-mood disorders (5,18). Meta-analytic estimates indicate a 2.7-fold increased risk of any mental health disorder and a 4-fold risk for any affective disorder in OBPD compared to offspring of healthy parents. However, these estimates are largely derived from historical cohorts identified in the previous century (19). The risk profile of OBPD also appears to be distinct from trajectory of risk for offspring of parents with major mood

disorders (20) or non-affective psychoses (21). This suggests that the risk endophenotypes in OBPD is not reducible to a generalised risk attributable to being raised by a parent with a mental health disorder (22), but may represent a specific vulnerability linked to OPBD status.

Although there is growing evidence that a substantial proportion of OBPD will develop at least one psychiatric disorder (23-26), there is scant evidence regarding the developmental progression of the syndromes presented in this cohort (27,28) and the existing literature is inconsistent with regard to the specificity of risk in OBPD (29). Data on protective factors are also very limited.

Developmental Modelling of OPBD Risk

Developmental modelling of risk of onset of BD highlights the importance of depressive, anxiety and/or behavioural disorders as potential precursors to BD in OPBD (30). However, these precursor disorders are neither necessary for, or specific to development of BD in OPBD. Indeed, existing longitudinal data on OPBD outcomes across different developmental periods reports diverse patterns with regards to continuity/discontinuity and specificity of psychopathology between different developmental stages. These findings indicate significant increases in the onset of depressive, anxiety and behavioural problems from early to late childhood (31), but very few new onset, recurrent and chronic disorders are reported from early to late adolescence (32). Ten -year longitudinal data also suggests developmental discontinuity in internalising problems in OPBD from early childhood to late adolescence, with these difficulties being expressed differently across periods, e.g. self-regulatory deficits in childhood through to thought problems (28). Longitudinal studies reporting prospective data for cohorts followed through different developmental stages, and data incorporating the peak risk point for BD onset (early adulthood) have only recently emerged (23,27,21,33). Consequently, it is unclear whether the presence of other disorders in this cohort represent early risk phenotypes, comorbid conditions, or early expressions of BD (e.g. ADHD; 29). In addition, the OPBD literature is hampered by methodological differences in terms of cross-sectional versus longitudinal designs, differences in assessment tools and sample recruitment (17), and differences in health care systems and provision (33,34).

As such the current 'state of the art' offers inconclusive findings regarding the predictive association of mood or non-mood disorders with the development of BD in OPBD. In addition, the issue of identification and treatment of psychopathology in OBPD raises a number of ethical questions, including whether identification of putative risk endophenotypes are sufficient and specific enough to merit early treatment with psychotropic medication (35), and whether identification using an endophenotype increases risk of false-positive diagnoses.

Clinical Stage Modelling: A Developmental Psychopathology Framework

One heuristic framework to improve the modelling of risk and onset of psychopathology is clinical staging. This framework proposes that disorders develop through a predictable temporal pathway and that stage-appropriate treatment can modify and potentially prevent such course (36,37). These models are usually conceptualised as stages, evolving from an at-risk stage (Stage 0; e.g. genetic predisposition) to an end-stage (Stage 4; e.g. highly severe and poor prognostic presentation of a disorder; 38); albeit with the understanding that all stages have an indicative character and may not describe the clinical course for any given individual (39). Consequently, clinical staging has been identified as a promising approach in understanding the risk endophenotype in OPBD (27,40,41); with a recent review of BD staging in adulthood highlighting its utility, evidence-based focus and dissemination to clinical settings (42).

To date, staging models of BD primarily apply two approaches for describing the progression of risk, focusing on either number of episodes (43) or on level of functioning (44,45). In both approaches the emphasis is mainly on the progress of the illness *following* the onset of manic-depressive symptoms and *only* in adult populations. In contrast, Duffy and colleagues (27,40,41) apply a clinical staging model focused on child and adolescent OPBD evaluated from *before* the onset of the first manic/hypomanic episode. As illustrated in Figure 1, this staging model progresses from a 'well' state (no presentation of mental health disorders; Stage 0), to the onset of non-mood disorders (Stage 1; e.g. anxiety, sleep disorders), followed by the onset of minor mood disorders (Stage 2; e.g. adjustment disorders) in childhood. The next stage is characterised by the development of major mood disorders (Stage 3; major mood depression) in adolescence, and ultimately the onset of the first

manic/hypomanic episode during late adolescence/ early adulthood (Stage 4). This model also suggests a recurrent substance use disorder across the last two stages.

Although this developmental psychopathology model offers a framework for delineating the developmental progression of BD in OPBD, it is based in findings from only one cohort. Therefore, it remains unclear whether this developmental pathway is generalizable to other at-risk OPBD cohorts. In addition, clinical staging in OBPD is based on trajectories towards an end-state of BD, and may not encompass risk of other psychiatric disorders as end-states. However, this is to be balanced against the promise of clinical staging as a tool for integrating early, family informed assessment of risk, and of the potential for the introduction of early intervention strategies that have a positive risk/benefit ratio for young people (e.g. psychological interventions or family therapies).

Aims of Review

Based on the existing evidence of increased risk of BD in OPBD, and of the presence of precursor disorders within the pathway to disorder, the aim of the current review was to systematically review and synthesise the existing literature on psychiatric risk in OPBD. In addition, where applicable, these data were compared to the clinical staging model of OPBD (40) with the aim of identifying an ultra-high-risk OPBD endophenotype. Specifically, we sought to establish whether there is a distinct pattern of psychiatric risk in OPBD; to establish how this risk profile differs according to developmental stage; and to evaluate whether a clinical staging model could provide a framework for understanding risk in OPBD.

Methods

Search Strategy

This systematic review was registered in PROSPERO (registration number: 42016048333; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048333). Conduct and reporting of the systematic review followed PRISMA guidelines (59). A search strategy was conducted independently by two reviewers (AR, SO) for articles published in peer-reviewed journals from 1970 to May 2016 and in press using the following electronic databases: EMBASE (1974-May 2016), PsychINFO (1806-April

2016) and Medline (1946- April 2016). Investigation was facilitated by OVID multi-field search. Hard copies were sought when necessary. After consultation with a librarian, the following terms were used to identify eligible papers: (child* or offspring* or son* or daughter*) AND (bipolar or mania or manic-depress*) adj5 (parent* or mother* or father*). No term was applied regarding the outcome of the studies (e.g. psychopathology or risk), to avoid elimination of studies due to word bias. Truncation (*) and adjacency operator ("adj5") were employed to increase search sensitivity. Citations from the initial research were de-duplicated. Full search history is reported in the Supplemental Material (Table 6). A leakage strategy was implemented through screening reference lists of all the eligible papers and existing narrative (12) and related systematic reviews (17-19,29,47).

Study Selection

Studies were included if they reported (i) a diagnostic assessment of BD in parent(s) based on a clinical interview; (ii) measures of psychopathology in offspring of parent(s) with BD based on Diagnostic and Statistical Manual (DSM); and (iii) a mean age of offspring below 18 years old at initial point of offspring psychiatric assessment (where studies reported on longitudinal follow-up studies, mean age was judged from the mean age at first assessment, but further follow-up points were included). Papers were eligible for inclusion if they were (iv) published in peer-reviewed journals, and (v) conducted between 1970 and May 2016.

Papers were excluded if they reported (i) on first degree relatives or members of extended families without distinguishing the offspring outcomes based on the relation to the affected member. This exclusion was used to ensure papers were focused on parent-offspring risk, rather than broad genetic risks. Papers were also excluded if (ii) reporting solely on dimensional outcomes in offspring. This was set to ensure a homogeneous and validated base of comparison between studies in terms of outcomes. (iii) Single or family case reports; (iv) book chapters, protocols, comments, corrections; and (v) previous systematic reviews and meta-analyses were also excluded.

Once titles and abstracts were screened, full texts of potentially eligible papers were examined. Where multiple papers were published from the same cohort, the article reporting most recent follow-up was selected. If remaining papers from these multi-

paper cohorts provided supplementary information about the cohort, they were also included. Some of these cohorts also reported follow-up points beyond the cohort mean age of 18 years. Consequently, for completeness, we reported these data for young adulthood and adulthood in our results. Accuracy of the final list of papers was confirmed by the independent reviewer SO and any disagreements resolved by consensus agreement with the third researcher (AM).

Data Extraction

Data were initially extracted per study and subsequently grouped per cohort. The following information was included in the final data collection: name of cohort and name of first author, year of publication, country of origin, parental characteristics (number and gender), offspring characteristics (number, gender and mean age), assessment characteristics (type of diagnostic criteria used, assessment tool used in parents, assessment tool used in offspring), design of study (cross-sectional or longitudinal, including the follow-up duration measured in years) and, if any, type of control group (i.e. offspring of healthy and/or psychiatrically ill parents).

Cohort findings were synthesized based on two developmental frameworks. In the first, cohorts were divided into five developmental stages based on the mean age of their sample: early childhood (0-6 y.o.); middle childhood (6-12 y.o.); adolescence (12-18 y.o.); young adulthood (18-23 y.o.) and adulthood (>23 y.o.). Psychiatric outcomes in OPBD were obtained in the form of lifetime/ current estimated prevalence (%) or cumulative incidence (%) for any Axis I disorder and then further distinguished for each mood and non-mood disorder. In the second framework (based on Duffy's clinical staging model, 27,40), available data on the mean age of the onset of mood and non-mood disorders were placed on a continuum according to their sequential relation to the onset of BD or manic/hypomanic symptoms. Longitudinal data reporting on the association between onset of mood and non-mood disorders and later onset of BD were also identified.

Quality Assessment

Quality assessment was conducted using an adapted version of the Agency for Healthcare Research and Quality (AHRQ) checklist (48). The quality check was applied to all papers that met inclusion criteria, regardless of the cohort. Methodological robustness of the papers was evaluated based on 11 quality criteria.

The rating scale is presented in detail in Table 7 (Supplemental Material). The grading of each item contained the options 'Yes' (2 points), 'Partially' (1 point), 'No' (0 points), or 'Not Applicable' (N/A). All applicable items were added up to a "Total Score", which was then divided by the "Max Score" (if all items applicable: 22 points, if 1 item not applicable: 20 points, if 2 items not applicable: 18 points, etc.), to calculate the "Percentage Score".

The formula used was:

$$Percentage\ Score = \frac{Total\ Score}{Max\ Score} \times \frac{x}{100}$$

Ten of the 26 eligible papers (39%) were independently rated by another member of the research team (SO). Inter-rater reliability was computed using "ReCal2", which resulted in a Cohen's Kappa score of 0.695, indicating a substantial agreement rate (49). Any discrepancies were reassessed and a consensus agreement was reached between all authors.

Results

Based on the systematic search described above, 1371 citations were identified, of which 61 full texts were reviewed. A further 6 articles were detected through hand-searching of reference lists of included articles. A total of 26 papers met inclusion criteria, representing 21 individual cohorts. The study selection process is illustrated in Figure 2.

Cohort Characteristics

Key study characteristics are presented in Table 1. The total number of the sample was measured based on the number of cohorts (for cohorts providing multiple papers, only the report with the most participants was considered). The total sample comprised n=1332 bipolar parents and n=2022 OPBD individuals. Sample size for individual studies ranged from n=7 to n=236 for parents with BD and from n=7 to n=391 for OPBD cohorts. In three of the cohorts, OPBD were strictly selected from independent families (i.e. one offspring per family). Among those cohorts reporting gender distribution, 11 of 19 indicated an equal male/female ratio (±10%) for BD parents and 16 of 20 indicated similarly equal distributions for OPBD. Males were the minority in almost all remaining cohorts. Included cohorts represented data from 8 countries: USA (k=13, including the Amish cohort), Canada (k=1), Netherlands (k=1), Switzerland (k=1), Spain (k=2), Turkey (k=1), Brazil (k=1) and Romania (k=1).

With regards to study design, 13 of the 21 cohorts had a cross-sectional design, 6 had a longitudinal design, and 2 cohorts generated reports using both designs. OPBD follow-up duration extended from 1 to 16 years beyond the index psychiatric assessment of offspring, therefore some samples exceeded the mean age of 18 years at the last assessment. The mean age of offspring ranged from 2.4 to 28 years old. Of the 16 cohorts with a control group, 10 were recruited from healthy parents ("healthy control group"), 1 from psychiatrically ill parents ("psychiatrically ill control group") and 5 from both ("both types control group").

Results from cohort studies were published between 1985 and 2016. This was reflected in the categorical measurement used: DSM-III or DSM-III-R (k=6), DSM - IV or DSM-IV-TR (k=14) and adaptation to both (k=1). Parental and offspring assessment tools differed slightly for each cohort, with SCID, SADS and K-SADS

being the predominant measures. There was considerable variability in how specific disorders were grouped in individual papers. Therefore, for our narrative synthesis, we generated a heuristic framework to map specific disorders into broad psychiatric categories. This is presented in Table 2. Six cohorts provided data for all diagnostic categories. The remaining cohorts provided data on some but not all the categories of psychiatric disorders covered in our review. Study findings were reported in the form of current prevalence (k=1), lifetime prevalence (k=19), cumulative incidence (k=2) or both lifetime and cumulative incidence (k=4; see Table 3).

Axis I Disorders across all Developmental Stages

Diagnostic data were available from all 21 cohorts, with 15 of the 21 cohorts reported data on the overall percentage of OPBD presenting with at least one DSM-III-or-IV Axis I diagnosis (Table 3; 23/50/51,32,61,24,13,26,60,20,57,21,59,34,58,62,53/33/52).). The remaining 6 cohorts reported data on DSM diagnoses, but did not correct for comorbid diagnoses, therefore a total percentage could not be generated (REFS). Approximately 50% of OPBD individuals in the majority of cross-sectional studies (21,26,34,50,57,58,60,62) and over 70% in longitudinal studies (23,32,33) were assessed as meeting criteria for at least one Axis I disorder. This risk was found to be elevated in OPBD when compared to offspring of healthy parents, regardless of developmental stage and country of origin (20,21,23,24,34,50,51,57,58,59). In the cohorts with a psychiatrically ill control group, 2 studies reported OPBD as having a greater rate of Axis I disorders (60,62), while 2 studies reported no difference between the two groups (20,21). Data for proportion of OBPD meeting criteria for mood and non-mood related disorders are reported in Table 3, further delineated by developmental period.

Early Childhood

Five cohorts (31,51,32,61,20) provided data for early childhood, with a mean age range from 2.4 (31) to 6 (20) years old. One cohort (51) had a healthy control group and one cohort (31) examined its sample at two time points (at a mean age of 2.4 and at a mean age of 5.6 years old).

Mood Disorders

Bipolar Spectrum Disorders (BPSD). A rate of 2% for BD not otherwise specified in OPBD was reported (51), which did not significantly differ from offspring of healthy parents.

Unipolar Spectrum Disorders (UPSD). The estimated prevalence in OPBD ranged from 0% (31) to 43% (61), which was not found to be significantly different from the healthy control group (51). Longitudinal analyses (31) showed a significant increase of depression incidence rates among OPBD over the course of early childhood.

Non-Mood Disorders

Anxiety Disorders (AD). The prevalence in OPBD ranged from 9% (31) to 43% (61). Only the prevalence of generalized anxiety disorder (GAD; 51) was found to be significantly higher in OPBD compared to the healthy control group. Longitudinal analyses (31) did not show a significant impact of time on OPBD's incidence rates of anxiety (mainly separation anxiety disorder: SAD).

Disruptive Behaviour Disorders (DBD). The prevalence rate ranged from 2% (51) to 43% (61) in OPBD. DBD (as a category, but also separately for attention deficit hyperactivity disorder and marginally for oppositional defiant disorder) were found to be more prevalent in OPBD compared to the control group (51). An increase in the incidence rates of OPBD's disruptive behaviour was observed during this developmental stage (31).

In all diagnostic categories (except for BPSD), the highest rate was reported by the Rockville cohort (61), which had a noticeably smaller sample size than the other cohorts (n=7 OPBD).

Country of origin

One of the 5 cohorts in this stage had a non-USA sample (20). No differences between non-USA and USA cohorts were observed.

Middle Childhood

Ten cohorts (31,55,25,32,24,13,26,60,20,50) provided data for the stage of middle childhood, with a mean age range from 6.4 (31) to 11.9 (50) years old. Four cohorts had a healthy control group (25,24,13,50) and three cohorts had a control group of both types (55,60,20). One cohort (31) examined its sample at two time points (at a mean age of 6.4 and at a mean age of 9.2 years old).

Mood Disorders

BPSD. The estimated prevalence in OPBD ranged from 2% (60) to 74% (13) and from 2% (20,50) to 37% (13) in cohorts specifically reporting for bipolar type-I disorder (BD-I). In both cases, the higher percentage belonged to the Cleveland cohort (13), which recruited its OPBD sample via clinical settings (i.e. in this cohort the offspring rather than the parents were presenting in clinical settings for treatment as opposed to most of the other included studies). The prevalence range without this cohort was 2% (60) to 38% (24) and 2% (20,50) to 16% (24) respectively. Five cohorts found a significantly higher prevalence of BPSD (55,24,13,50) and BD-I (55,25,50) in OPBD compared to the healthy control group. Two cohorts (60, 20) found no differences between the rates of OPBD and of healthy control group. Three cohorts found no differences between the rates of OPBD and of psychiatrically ill control groups (55,60,20).

UPSD. The prevalence rate in OPBD ranged from 5% (60) to 44% (31). Major depressive disorder (MDD) ranged from 2% (50) to 14% (24) and minor depressive disorders (i.e. dysthymia, adjustment disorder with depressed mood, depression not otherwise specified) from 6% (32) to 19% (20). In 2 cohorts, the OPBD's rates for any UPSD (25,20) and specifically for MDD (20,50) were higher compared to the healthy control group. In 5 cohorts, OPBD's rates for any UPSD were not found to be significantly higher compared to the healthy (55,24,13,60) and the psychiatrically ill (55,60,20) control groups. One cohort (31) reported a significant effect of time (i.e. an increase of depressive symptoms in OPBD during this developmental stage).

Non-Mood Disorders

AD. The estimated prevalence in OPBD ranged from 1% (13) to 44% (55,60). In 2 of the 4 cohorts with a healthy control group the prevalence of any AD was significantly higher in OPBD (25,50). In 2 of the 3 cohorts with both types of control group (55,60) OPBD presented a significantly higher prevalence of any AD when separately compared with offspring of psychiatrically ill parents and with offspring of healthy parents; meanwhile in the 3rd cohort, rates of AD were only significantly higher when compared to the healthy control group (20). SAD (55,60,25,20,50), GAD (25,50), social phobia (SOP) (50,55,60), specific phobias (SP) (60) and obsessive-compulsive disorder (OCD) (25) were also found to be significantly higher compared to the

cohort's control groups. Longitudinal analyses (31) confirmed a significant increase in anxiety symptoms during this developmental stage.

Attention Deficit Hyperactivity Disorder (ADHD). The estimated prevalence in OPBD ranged from 4% (13) to 31% (24). Three cohorts found a higher incidence of ADHD in OPBD compared to a healthy control group (25,24,50), 1 cohort compared to a psychiatrically ill control group (55), and 1 cohort compared to offspring of healthy and non-healthy parents as a single control group (60). Two cohorts reported no significant differences compared to any of the control groups (13,20).

Oppositional Defiant Disorder (ODD)/Conduct Disorder (CD). The prevalence rate in OPBD ranged from 0% (13) to 28% (31). For cohorts reporting separately for ODD and CD the ranges were 7% (60) to 19% (25) and 2% (32) to 7% (60) respectively. Two cohorts observed an increased prevalence in OPBD compared to a healthy control group (24,50: only for ODD), and 1 cohorts compared to its combined control group (for ODD and CD; 60). Four cohorts did not find any differences between (55,25,13,20) and within (i.e. longitudinally; 31) their sample.

Substance Use Disorders (SUD). The prevalence rate in OPBD ranged from 0% (25,13) to 9% (20). No significant difference was found in the SUD incidence between OPBD and any type of control group (25,13,20).

Country of origin

Two of the 10 cohorts in this stage had a non-USA sample (60,20). The non-USA cohorts reported relatively smaller prevalence rates of BPSD in OPBD (2% and 4% respectively) compared to the USA cohorts (in all cohorts ≥9%). Neither study reported a significant difference in the prevalence of BPSD when compared to the control group as opposed to the USA cohorts (55,25,24,13,50).

Adolescence

Thirteen cohorts (25,20,50,57,21,59,34,56,58,32,52,62,30) provided data on the adolescent developmental stage, with a mean age range from 12 (25,20,50) to 17.9 (62) years old. Five cohorts had a healthy control group (25,57,34,58,30), 1 cohort a psychiatrically ill control group (62), and 2 cohorts had both types control group (20,21). In this developmental stage, 1 of the cohorts (34) assessed its sample on current disorder prevalence and therefore it is reported separately.

Mood Disorders

BPSD. The estimated prevalence in OPBD ranged from 0% (21,32) to 27% (62) and from 6% (59) to 7% (30) in cohorts specifically reporting for BD-I. Two cohorts with a healthy control group (25,30) and 1 with a psychiatrically ill control group (62) reported a significant difference between the groups, with OPBD presenting an increased risk for BPSD (25,52), BD-I (30) and cyclothymia (62). Two cohorts with a healthy control group (57,58) and 1 with both types of control group (21) found no difference in BPSD prevalence between the groups. The current prevalence of BPSD in the Bucharest cohort (34) was 1% and was not found to be significantly different from the healthy control group.

UPSD. The lifetime estimated incidence in OPBD ranged from 16% (58) to 34% (25), while the current prevalence was 8% (34). MDD ranged from 3% (62) to 22% (32) and minor depressive disorders from 3% (59) to 39% (32). Four cohorts found a significant higher risk of UPSD in OPBD when compared with a healthy control group (25,28: for any mood disorder, 21: only for MDD, 34: current prevalence). Two cohorts reported no significant differences in the estimated prevalence of any UPSD between OPBD and healthy control group (57,58) and another 2 between OPBD and psychiatrically ill control group (21,62).

Non-Mood Disorders

AD. The lifetime prevalence in OPBD ranged from 3% (59) to 46% (20,56), while the current prevalence was 12% (34). Three cohorts reported a significantly higher risk in OPBD for any AD (34: current prevalence,20,25) and specifically for SAD (25), GAD (25) and OCD (25) when compared to the healthy control group. The remaining cohorts did not observe any differences between OPBD, healthy (57,21,58), and/or psychiatrically ill control groups (21,62) in AD prevalence.

ADHD. The lifetime incidence of OPBD ranged from 5% (52) to 40% (27), while the current incidence was 21% (34). Three cohorts (25,21,34: current prevalence) found a significantly higher rate of ADHD in OPBD compared to a healthy control group. Two cohorts found no difference in the rate between OPBD and healthy control group (57,58) and one cohort between OPBD and psychiatrically ill control group (21).

ODD/CD. The lifetime prevalence in OPBD ranged from 3% (21) to 34% (56) and specifically for ODD and CD: 12% (57) to 28% (25) and 3% (59) to 8% (58)

respectively. Current prevalence of ODD and CD in OPBD was 3% and 11% respectively (34). No cohort with a control group of any type reported a significant difference between the groups (25,57,21,34,56,62).

SUD. The prevalence in OPBD during adolescence ranged from 2% (57) to 19% (62), with no cohort reporting a significantly higher risk in the OBPD group compared to controls (25,57,58,62).

Country of origin

Six of the 13 cohorts in this stage had a non-USA sample (20,57,21,34,58,52). The main difference compared to the USA cohorts was observed in the diagnostic category of BPSD. Non-USA cohorts reported a prevalence of under 5% and non-significant difference compared to control group in contrast to the USA cohorts that reported a prevalence of above 7% (in 4/5 cohorts) and a significantly higher risk for OPBD (25,62,30).

Early Adulthood/Adulthood

Seven cohorts (50/23,32,25,20,53-33,54,27) provided psychiatric follow-up data for early adulthood/adulthood with a mean age range from 18 (50) to 28 (33) years old. Three cohorts had a healthy control group (50/23,25,27) and 1 cohort had a control group of both types (20/54).

Mood Disorders

BPSD. The prevalence rate in OPBD ranged from 18% (50) to 33% (25) and for BD type I or II: 4% (23) to 17% (54). All four cohorts with a control group reported a significantly higher risk for BPSD, BD-I and BD-II in OPBD compared to a healthy control group (23,25,27) and a psychiatrically ill control group (54).

UPSD. The prevalence of MDD in OPBD ranged from 10% (53) to 37% (54) and of minor mood disorders from 9% (54) to 30% (27). One cohort observed a higher risk in OPBD compared to the healthy control group for both categories (23), 1 cohort for none of the categories (54), and 1 study only for MDD (27). There were no differences reported compared to the psychiatrically ill control group (54).

Two cohorts reported over half of their sample to experience or have experienced any UPSD (25) and any mood disorder (BPSD and UPSD; 20) in their lifetime. This was found to be significantly higher than the healthy control group (25,20).

Non-Mood Disorders

AD. The lifetime prevalence in OPBD ranged from 10% (25) to 48% (20). Three of the four cohorts found a significantly higher prevalence of any AD (23,27), SAD (23,25), GAD (23,25), SOP (23), panic disorder (PD) (23) and OCD (25) compared to the healthy control group.

ADHD. The lifetime prevalence in OPBD ranged from 5% (53,33) to 22% (25). Two cohorts found a significantly higher risk in OPBD compared to a healthy control group (23,25). Two did not find a higher risk compared to both healthy (54,27) and psychiatrically ill control groups (54).

ODD/CD. The lifetime prevalence in OPBD ranged from 2% (27) to 7% (33,53). For ODD: 15% (54) to 33% (25) and for CD: 10% (23) to 12% (54). Only 1 (23) of the 4 cohorts with a control group, reported a significantly higher risk in OPBD (vs healthy group and only for ODD).

SUD. The lifetime prevalence in OPBD ranged from 14% (25) to 30% (27). Two of the cohorts reported an increased risk compared to the healthy control group (23,27). Two did not find any difference (25,54) compared to the control groups.

Country of origin

Four of the 7 cohorts in this stage had a non-USA sample (20,53/33,54,27). The main differences were spotted in the non-mood disorders where overall the non-USA cohorts reported non-significant differences between OPBD and control groups in contrast to the USA cohorts.

Disorder Onset and Clinical Staging Findings

Two approaches to staging were observed in the literature: staging by reporting of rates of disorder or mean age of onset of symptoms prior and/or subsequent to onset of BD, and staging by examination of associations between disorders at one point and their association with disorder onset at subsequent developmental points. The former approach is a less rigorous approach to staging given that mean age masks variance in age of onset within cohorts; nevertheless, based on the state of the art of the existing literature, we opted to report both staging models so as to gain an insight into broad patterns of developmental risk in OPBD.

Seven of the cohorts reported data on the onset of mood and non-mood disorders in OPBD (23,25-27,30,33,56). Data was reported either in the form of mean age of onset of the disorders (cross-sectional cohorts: 25,56,26) and/or of the percentage of OPBD exhibiting any given psychiatric disorder prior to onset of BD (longitudinal cohorts: 30,27,33,23).

In 2 of the 3 cross-sectional cohorts (25,56) the following pattern of mean age of disorder onset was observed in OPBD: non-mood disorders (ADHD, anxiety and behavioural disorders); mood disorders (depression, MDD);mania.

In the 4 longitudinal cohorts the clinical progression of disorders reported for OPBD developing BD was the following: non-mood disorders (ADHD, anxiety, behavioural and sleep disorders) prior to the 1st episode of mania/hypomania (30,27,33,23) and prior to mood disorders (30,27); non-bipolar mood disorders (especially those in the depressive polarity) prior to mania/hypomania (30,27,33,23); mania/hypomania; and substance use disorder prior (23) or subsequent (27,33) to the 1st hypomanic/manic episode.

The developmental stage of each psychiatric category onset varied considerably, with USA cohorts (25,56,26,23) presenting an overall earlier mean onset of disorders compared to non-USA and the Amish cohorts (30,27,33). Specifically, all USA cohorts (23,25,26,56), except for the Amish cohort (30), reported a pre-pubertal mean age of onset of mania/hypomania, or a substantial percentage of OPBD (86%) exhibiting the first (hypo)manic episode in childhood (before 12 y. o.). Non-USA cohorts (27,33) and the Amish cohort (30) reported a mean age of onset of the first BD activation episode in late adolescence/young adulthood.

Among the longitudinal cohorts that examined cross-lagged associations between a precursor disorder at one developmental point and later onset of (hypo) mania, childhood anxiety was most consistently related to later manic symptoms (27,30). The mean onset of anxiety disorders was almost 10 years prior to the onset of (hypo) mania (27,30). In the Pittsburgh cohort (23), DBD, MDD and subthreshold manic/ hypomanic episodes were significantly associated to the onset of (hypo)mania. However, when statistical analysis was limited to prospective data (for 344/391 participants), only the subthreshold manic/hypomanic episodes continued to report significant prediction for the development of BD in OPBD.

Quality Assessment Results

An assessment of methodological quality for all studies included in the review is presented in Table 4 with reporting per AHRQ item and for total score. Papers' percentage score ranged from of 56% (59) to 90% (50,51) with a mean of 73% (SD=9,9%). The highest scores for methodological quality were reported for the Pittsburgh (23,50,51) and Lausanne cohorts (20,54). The lowest score for methodological quality was reported for the Texas cohort (59). Across all studies, the main methodological inconsistency was in reporting of sample size, with only 1 study (54) conducting and reporting a power analysis, although this may represent omission of reporting rather than inadequate power. In addition, only 7 (23,24,30,34,50,51,61) of the 20 controlled studies attempted to reduce bias of baseline differences between study and control groups and 4 (20,25,31,54) of the rest did so partially (usually recruiting the control group based on the same geographical areas). Outcome assessment of offspring psychopathology was blind in 16 (13,20,21,23-25,27,30,34,50,51,54,55,60-62) of the 27 studies and partially blind in another 2 (31,32), due to the failure in maintaining blindness of parental psychiatric status during the follow-up assessment. The rest of the quality checklist items showed less heterogeneity, with most studies using a reliable and validated method for measuring parental and offspring psychopathology and adequate descriptions of the cohort characteristics.

Discussion

The current systematic review synthesizes evidence indicating an increased risk of developing a wide range of mood and/or non-mood disorders in OPBD in comparison to offspring of non-bipolar parents. Our findings update and extend previous reviews (12,18,19), and suggest there is additional benefit to appraising this risk through a developmental framework. As hypothesized, risk of psychiatric disorder in OPBD progresses along a developmental pattern, and data are broadly supportive of a clinical staging model.

As indicated by previous findings (18), we report consistently high rates for OPBD experiencing any Axis I disorder across all developmental stages. However, this broadly elevated risk, obscures a more complex pattern of risk of specific disorders

when the estimated risk and the mean age of onset of specific disorders are placed along a developmental continuum. Our revised model (Figure 3) updates previous clinical staging models; (27) by proposing that developmental risk in OPBD evolves from non-mood disorders in childhood to mood and manic/hypomanic symptoms accompanied by recurrent substance use disorders in adolescence and early adulthood. However, we note that the current evidence for risk in OBPD is still reliance to a large extent on cross-sectional data within time periods, and that the data on true clinical staging - i.e. modelling of a sequential pattern of risk across developmental periods to a number of 'end-state' psychiatric disorders (including BD) – is still limited. Therefore, our discussion focuses on the broad patterns of developmental risk identified in the review.

Clinical Stage 1: Non-Mood Disorders

Consistent with earlier models (27,40), Stage 1 is characterized by the onset of non-mood disorders in OPBD during early and middle childhood. These findings support possible neurodevelopmental vulnerabilities in OPBD (29). However, although OPBD are reported as vulnerable to a number of anxiety and behavioral disorders (ADHD/ODD/CD) during this developmental stage, our synthesis of the longitudinal data suggests that to date, only anxiety disorders are predictive of later BD onset (27,30). Therefore, although anxiety disorders are viewed are a precursor in most OPBD cases that go on to develop BD, not all OPBD's who have anxiety in childhood go on to develop BD. Consequently, anxiety may not be robust as indicator, unless supplemented by additional data on other risk factors.

Clinical Stage 2-3: Mood Disorders

In contrast to earlier models (27,40), our synthesis suggests that developmental risk in adolescence may be more accurately represented by a broad "Mood Disorders" stage, without delineation into minor and major non-bipolar mood disorders. This may be more parsimonious, given that the current review identifies no significant differences between estimated prevalence and onset of minor (dysthymia, adjustment disorder with depressed mood, and DD NOS) and major (MDD) mood disorders in OPBD. We also emphasize that mood disorders, particularly depressive disorders, consistently precede the onset of manic/hypomanic episodes both in longitudinal and cross-sectional studies (23,25,27,30,33,56). In contrast to previous papers (27,40) we

synthesized both prospective and retrospective data, and as such, we suggest that a broader mood disorders category may have greater clinical utility than delineation into narrower bandings. However, we also note that particularly this stage relies upon a combination of developmentally sensitive measurement tools (e.g. K-SADS-PL, K-SADS-E) and recall bias of informants (typically parents for children under 16 y.o.), that may influence the identification of minor internalizing symptoms retrospectively, especially when followed by externalizing and major disturbances (33,66). Moreover, although evidence suggests that manic symptoms are more accurately reported by caregiver reports than by self- or teacher reports (67), in OPBD samples parental mental state may be a confound in assessing OPBD functioning and health status (68,69). We also note that labelling of mood and anxiety disorders vary considerably between studies (e.g. unipolar depression, minor depressive disorder, major depressive disorder) and as such it may be difficult to identify clear patterns for specific sub-classes of non-bipolar mood disorder in OPBD until further large datasets emerge.

Clinical Stage 4: Mania/Hypomania

Consistent with existing models (27,40) our review supports a final stage (Stage 4) representing the onset of "Mania/Hypomania", for some OPBD individuals. Similar to our concerns regarding labelling of mood disorders we also note that the existing literature uses the terms BD, BPSD and Mania/Hypomania interchangeably. This introduces a potential lack of specificity regarding sub-type of BD assessed and separation first manic/hypomanic symptoms from BD onset. There are also implications for diagnostic accuracy, given that index incidence of mood symptoms in BD often occurred via a depressive episode (23,27,33). We suggest that specificity of the predictive utility of this stage will increase as more cohorts report adult follow-up data.

We also observed that our findings indicate a divergence in the mean age of BD onset between USA and non-USA OPBD cohorts, suggesting that sociocultural background could be a moderating factor in the development of BPSD. It is possible that findings may differ in USA cohorts due to reporting bias related to the assessment of broader, subthreshold bipolar spectrum syndromes (i.e. BDNOS); sample selection bias related to mental health system accessibility (33); and increased prescription of antipsychotic

and mood stabilizing drugs for underage individuals in USA (70). This highlights that cultural aspects in the aetiology and reporting of risk may also be relevant.

Recurrent Substance Use Disorder

We identified a gradual increase from middle childhood to early adulthood in substance use disorder (SUD) amongst OPBD, along with an elevated risk compared to offspring of healthy parents during the last developmental stage. In addition, based on preliminary clinical staging data stemming from longitudinal studies (23,27,33) , our review provides evidence for SUD co-occurring with BD with an onset either prior or subsequent to the onset of manic/ hypomanic symptoms. Elevated prevalence of comorbid SUD and BPSD has been documented both in community (71-73) and clinical studies (74,75) and longitudinal studies following OPBD from childhood to early adulthood have underlined that risky behaviors may be a marker pf emergent psychiatric disorder in OPBD (76). Shared mechanisms and overlapping neurobiological pathways such as impulsivity, susceptibility to behavioral sensitization, impaired coping skills, and responses to rewarding stimuli suggest a complex bidirectional interaction between SUD and BD (77,78). Substance use has been proposed to increase the risk of BD development by "unmasking" subthreshold symptoms to a clinically significant level (79,80); inversely, substance use has been theorized as a method of coping with unpleasant affective symptoms ("self-treatment strategy"; 81,82). Both SUD and BD may also be triggered by stressful life events (83,84), potential via epigenetic mechanisms.

Regardless of directionality, comorbid substance use is associated with a more complicated diagnosis, prognosis and treatment of BD (85) and the presence of SUD may obscure the diagnosis of BD, as intoxication by or withdrawal from substances can mimic depressive, manic and anxious states (86). Therefore, our data support a need for integrating assessment and if indicated early intervention for SUD in OPBD may confer benefits for management of broader psychiatric disorder in this high-risk group.

Limitations

There are a number of limitations in the present review. Firstly, the developmental patterns of risk found to occur in OPBD, should be interpreted with caution as most of the included studies have a cross-sectional design, and the majority of OPBD have not

yet passed through the peak risk period for developing BD. Secondly, the methodological heterogeneity of studies may have influenced the overall findings; specifically small sample sizes and the lack of control groups in some of the cohorts, may have substantially inflated estimates of risk of psychopathology in OPBD. Nevertheless, our quality assessment of the literature indicated a methodologically robust corpus of studies. Thirdly, the exclusion of dimensional outcomes in OPBD, although applied in order to ensure a comparable baseline between studies, also resulted in omission of subthreshold symptoms BD symptoms (e.g. 13). Finally, although we identified studies from Canada, USA, South America, Europe and Western Asia, our own inclusion criteria and the current status of the field may limit the cross-cultural validity and applicability of our findings to the global youth.

Implications for Research

Our review underline the importance of developmental continuity in understanding the risk of psychopathology and adoption of a developmental framework when assessing at-risk cohorts. However, upscaling developmental research in ultra-high-risk offspring requires tighter methodologies. For instance, assessment and reporting of the mean age of onset of a disorder and of the current estimated prevalence would enable researchers to better delineate risk at specific developmental stages. In addition, using combined data from complementary sources of information (e.g. caregivers, teachers, self-reports) could enhance the accuracy of findings (68,69).

Our evidence supports and extends existing developmental psychopathology frameworks (27,40). However, bearing in mind the limited available data and heterogeneity of the studies included in this systematic review, further research is required to improve the evidence-base and generalizability of this model, particularly with regard to longitudinal cohorts. This would enable the field to more confidently comment on continuity/discontinuity of risk between developmental periods and also relate developmental findings to outcomes for the peak risk period for BD onset as has been noted for the literature on risk in offspring of schizophrenia-diagnosed parents (64,65). Furthermore, there is a parallel literature on neurophysiological markers for BD risk endophenotypes (87-89). In this regard, OPBD cohorts offer an ideal research opportunity for examining the role of (i) the underlying epigenetic mechanisms in OPBD according to developmental stage (ii) the mediating and moderating factors contributing to the development of BD (e.g. sociocultural

background and substance use, as suggested by this review), and (iii) the resilience/protective factors of OPBD presenting no clinical symptoms.

Implications for Clinical Practice

With regards to clinical implications, our review reiterates the value of considering family mental health status of individuals as markers for both risk and resilience. Health professionals (including but not limited to mental health) engaging with adult BD-diagnosed individuals, but also with children and young people, should be aware of the high-risk profile of OPBD and its dynamic nature through development.

Parents with BD and co-caregivers should also be provided with information about the factors that may set their offspring at-high-risk for developing maladaptive behaviors, encouraged to seek professional help if necessary, and offered a systematic support and psychoeducation for maintaining the balance between parenting and mental health issues. Additionally, children and young people presented in clinical settings that are offspring of parents with BD should be monitored for potential early markers of risk, and offered early intervention where indicated. The clinical staging model thus offers a promising framework for utilizing developmental "opportunity windows" linked to optimally needs-matched interventions (42). For instance, our preliminary evidence indicating childhood anxiety disorders and depression in adolescence as potential early markers of BD in OPBD (23,27,30,33), offers the opportunity for development and implementation of psychological interventions, including caregivers where appropriate, over medication prescription, given the association of antidepressants and stimulants to the onset of BD (70). Finally, a move towards early intervention and primary prevention within OPBD, would link to broader strategies acknowledging the public health importance of mental health, both in the case of general and indicated interventions.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

2. Kleine-Budde K, Touil E, Moock J, Bramesfeld A, Kawohl W, Rössler W. Cost of illness for bipolar disorder: a systematic review of the economic burden. Bipolar disorders. 2014;16(4):337-353.

3. Fajutrao L, Locklear J, Priaulx J, Heyes A. A systematic review of the evidence of the burden of bipolar disorder in Europe. Clinical Practice and Epidemiology in Mental Health. 2009;5(1):1.

4. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2013;380(9859):2163-2196.

5. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry. 2005;62(6):593-602.

6. Pompili M, Gonda X, Serafini G, Innamorati M, Sher L, Amore M, Rihmer Z, Girardi P. Epidemiology of suicide in bipolar disorders: a systematic review of the literature. Bipolar disorders. 2013;15(5):457-490.

7. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA, STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biological psychiatry. 2004;55(9):875-881.

8. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of general psychiatry. 2007;64(5):543-552.

9. Scott J, Leboyer M. Consequences of delayed diagnosis of bipolar disorders. L'Encéphale. 2011;37:S173-175.

10. Hirschfeld RM, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. The Journal of clinical psychiatry. 1899;64(2):161-174.

11. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of general psychiatry. 2012;69(3):220-229.

12. Chang K, Steiner H, Ketter T. Studies of offspring of parents with bipolar disorder. American Journal of Medical Genetics Part C: Seminars in Medical Genetics 2003 Nov 15 (Vol. 123, No. 1, pp. 26-35). Wiley Subscription Services, Inc., A Wiley Company.

13. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Demeter CA, Bedoya D, Kahana SY, Calabrese JR. Early symptoms of mania and the role of parental risk. Bipolar Disorders. 2005;7(6):623-634.

14. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Archives of general psychiatry. 2003;60(5):497-502.

15. Craddock N, Jones I. Genetics of bipolar disorder. Journal of medical genetics. 1999;36(8):585-594.

16. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically ill parents. Archives of General Psychiatry. 2010;67(3):252-257.

17. Duffy A, Doucette S, Lewitzka U, Alda M, Hajek T, Grof P. Findings from bipolar offspring studies: methodology matters. Early intervention in psychiatry. 2011;5(3):181-191.

18. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. Bipolar disorders. 2001;3(6):325-334.

19. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. The Canadian Journal of Psychiatry. 1997;42(6):623-31.

20. Vandeleur C, Rothen S, Gholam-Rezaee M, Castelao E, Vidal S, Favre S, Ferrero F, Halfon O, Fumeaux P, Merikangas KR, Aubry JM. Mental disorders in offspring of parents with bipolar and major depressive disorders. Bipolar disorders. 2012;14(6):641-653.

21. Sanchez-Gistau V, Romero S, Moreno D, de la Serna E, Baeza I, Sugranyes G, Moreno C, Sanchez-Gutierrez T, Rodriguez-Toscano E, Castro-Fornieles J. Psychiatric disorders in child and adolescent offspring of patients with schizophrenia and bipolar disorder: A controlled study. Schizophrenia Research. 2015;168(1):197-203.

22. Cicchetti D, Rogosch FA, Toth SL. Maternal depressive disorder and contextual risk: Contributions to the development of attachment insecurity and behavior problems in toddlerhood. Development and psychopathology. 1998;10(02):283-300.

23. Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB, Sakolsky D, Diler R, Hafeman D, Merranko J, Iyengar S. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. American Journal of Psychiatry. 2015;172(7):638-646.

24. Singh MK, DelBello MP, Stanford KE, Soutullo C, McDonough-Ryan P, McElroy SL, Strakowski SM. Psychopathology in children of bipolar parents. Journal of affective disorders. 2007;102(1):131-136.

25. Henin A, Biederman J, Mick E, Sachs GS, Hirshfeld-Becker DR, Siegel RS, McMurrich S, Grandin L, Nierenberg AA. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. Biological psychiatry. 2005;58(7):554-561.

26. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. Journal of the American Academy of Child & Adolescent Psychiatry. 2000;39(4):453-460.

27. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. The British Journal of Psychiatry. 2014;204(2):122-128.

28. Klimes-Dougan B, Long JD, Lee CY, Ronsaville DS, Gold PW, Martinez PE. Continuity and cascade in offspring of bipolar parents: A longitudinal study of externalizing, internalizing, and thought problems. Development and psychopathology. 2010;22(04):849-866.

29. Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. American Journal of Psychiatry. 2012;169(12):1247-1255.

30. Egeland JA, Endicott J, Hostetter AM, Allen CR, Pauls DL, Shaw JA. A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. Journal of affective disorders. 2012;142(1):186-192.

31. Radke-Yarrow M, Nottelmann E, Martinez P, Fox MB, Belmont B. Young children of affectively ill parents: a longitudinal study of psychosocial development. Journal of the American Academy of Child & Adolescent Psychiatry. 1992;31(1):68-77.

32. Hammen C, Burge D, Burney E, Adrian C. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Archives of general psychiatry. 1990;47(12):1112-1117.

33. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. American Journal of Psychiatry. 2013;170: 542-549.

34. Grigoroiu-Serbănescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V. Psychopathology in children aged 10–17 of bipolar parents:

psychopathology rate and correlates of the severity of the psychopathology. Journal of affective disorders. 1989;16(2):167-179.

35. Chang KD, Saxena K, Howe M, Simeonova D. Psychotropic medication exposure and age at onset of bipolar disorder in offspring of parents with bipolar disorder. Journal of child and adolescent psychopharmacology. 2010 Feb 1;20(1):25-32.

36. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Australian and New Zealand Journal of Psychiatry. 2006;40(8):616-622.

37. Passos IC, Kapczinski NS, Quevedo J, Kauer-Sant'Anna M, Kapczinski F. Staging models and functional outcomes in bipolar disorder: clinical implications. Current Treatment Options in Psychiatry. 2015;2(3):205-217.

38. Berk M, Berk L, Dodd S, Cotton S, Macneil C, Daglas R, Conus P, Bechdolf A, Moylan S, Malhi GS. Stage managing bipolar disorder. Bipolar disorders. 2014;16(5):471-477.

39. Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. Acta Psychiatrica Scandinavica. 1993;87(4):225-230.

40. Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. Journal of affective disorders. 2010;121(1):127-135.

41. Duffy A. Early identification of recurrent mood disorders in youth: the importance of a developmental approach. Evidence Based Mental Health. 2015;18(1):7-9.

42. Kapczinski F, Magalhães PV, Balanzá-Martinez V, Dias VV, Frangou S, Gama CS, Gonzalez-Pinto A, Grande I, Ha K, Kauer-Sant'Anna M, Kunz M. Staging systems in bipolar disorder: an international society for bipolar disorders task force report. Acta psychiatrica scandinavica. 2014;130(5):354-363.

43. Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, De Castella AR, Filia S, Filia K, Tahtalian S, Biffin F, Kelin K. History of illness prior to a diagnosis of bipolar

disorder or schizoaffective disorder. Journal of affective disorders. 2007;103(1):181-186.

44. Rosa AR, Magalhães PVS, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. Journal of Clinical Psychiatry. 2014;75(5):e450–6.

45. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vázquez GH, Vieta E, Berk M. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009;33(8):1366-1371.

46. British Medical Journal. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009;339:b2535. http://dx.doi.org/10.1136/bmj.b2535.

47. Frías Á, Palma C, Farriols N, Salvador A. Characterizing offspring of bipolar parents: a review of the literature. Actas espanolas de psiquiatria. 2015;43(6):221-34.

48. Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's disease and cognitive decline. Evidence Report/Technology Assessment No. 193. (Prepared by the Duke evidencebased practice center under contract No. HHSA 290-2007-10066-I). Agency for Healthcare Research and Quality: Rockville, MD. 2010.

49. Cohen JA. A coefficient of agreement for nominal scales. Educational and Psychological Measurement. 1960;20:37-46.

50. Birmaher B, Axelson D, Monk K, Kalas C, Goldstein B, Hickey MB, Obreja M, Ehmann M, Iyengar S, Shamseddeen W, Kupfer D. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring study. Archives of general psychiatry. 2009;66(3):287-296.

51. Birmaher B, Axelson D, Goldstein B, Monk K, Kalas C, Obreja M, Hickey MB, Iyengar S, Brent D, Shamseddeen W, Diler R. Psychiatric disorders in preschool offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring Study (BIOS). American Journal of Psychiatry. 2010;167:321-330.

52. Reichart CG, Wals M, Hillegers MH, Ormel J, Nolen WA, Verhulst FC. Psychopathology in the adolescent offspring of bipolar parents. Journal of affective disorders. 2004;78(1):67-71.

53. Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar disorders. 2005;7(4):344-350.

54. Preisig M, Strippoli MP, Castelao E, Merikangas KR, Gholam-Rezaee M, Marquet P, Aubry JM, Vandeleur CL. The specificity of the familial aggregation of early-onset bipolar disorder: A controlled 10-year follow-up study of offspring of parents with mood disorders. Journal of affective disorders. 2016;190:26-33.

55. Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF. Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study. Psychiatry Research. 2006;145(2):155-167.

56. Freed RD, Tompson MC, Otto MW, Nierenberg AA, Henin A. A latent class analysis of parental bipolar disorder: Examining associations with offspring psychopathology. Psychiatry research. 2015;230(2):314-322.

57. Garcia-Amador M, De la Serna E, Vila M, Romero S, Valenti M, Sanchez-Gistau V, Benabarre A, Vieta E, Castro-Fornieles J. Parents with bipolar disorder: Are disease characteristics good predictors of psychopathology in offspring?. European Psychiatry. 2013;28(4):240-246.

58. Erkan M, Gencoglan S, Akguc L, Ozatalay E, Fettahoglu EC. Attachment styles and psychopathology among adolescent children of parents with bipolar disorder. Medical science monitor: international medical journal of experimental and clinical research. 2015;21:1083-1088.

59. Zappitelli MC, Bordin IA, Hatch JP, Caetano SC, Zunta-Soares G, Olvera RL, Soares JC. Lifetime psychopathology among the offspring of Bipolar I parents. Clinics. 2011;66(5):725-730.

60. Petresco S, Gutt EK, Krelling R, Lotufo Neto F, Rohde LA, Moreno RA. The prevalence of psychopathology in offspring of bipolar women from a Brazilian tertiary center. Revista Brasileira de Psiquiatria. 2009;31(3):240-246.

61. Zahn-Waxler C, Mayfield A, Radke-Yarrow M, McKnew DH, Cytryn L, Davenport YB. A follow-up investigation of offspring of parents with bipolar disorder. Am J Psychiatry. 1988;145(4):506-509.

62. Klein DN, Depue RA, Slater JF. Cyclothymia in the adolescent offspring of parents with bipolar affective disorder. Journal of Abnormal Psychology. 1985;94(2):115-127.

63. Radke-Yarrow M. Children of depressed mothers: From early childhood to maturity. Cambridge University Press; 1998.

64. Yung AR, Stanford C, Cosgrave E, Killackey E, Phillips L, Nelson B, McGorry PD. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. Schizophrenia research. 2006;84(1):57-66.

65. Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis?. Schizophrenia research. 2011;125(1):62-68.

66. Carlson GA, Blader JC. Diagnostic implications of informant disagreement for manic symptoms. Journal of Child and Adolescent Psychopharmacology. 2011;21(5):399-405.

67. Youngstrom EA, Genzlinger JE, Egerton GA, Van Meter AR. Multivariate meta-analysis of the discriminative validity of caregiver, youth, and teacher rating scales for pediatric bipolar disorder: Mother knows best about mania. Archives of Scientific Psychology. 2015;3(1):112-137.

68. Youngstrom EA, Findling RL, Calabrese JR. Effects of adolescent manic symptoms on agreement between youth, parent, and teacher ratings of behavior problems. Journal of Affective Disorders. 2004;82:S5-16.

69. Tillman R, Geller B, Craney JL, Bolhofner K, Williams M, Zimerman B. Relationship of parent and child informants to prevalence of mania symptoms in children with a prepubertal and early adolescent bipolar disorder phenotype. American Journal of Psychiatry. 2004;161(7):1278-1284.

70. Uher R. Gene–environment interactions in severe mental illness. Frontiers in psychiatry. 2014;5:48.

71. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). Journal of the American Academy of Child & Adolescent Psychiatry. 2010;49(10):980-989.

72. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independentmood and anxiety disorders: Results from the national epidemiologic survey on alcohol and relatedconditions. Archives of general psychiatry. 2004;61(8):807-816.

73. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. Jama. 1990;264(19):2511-2518.

74. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar disorders. 2001;3(4):181-188.

75. Strakowski SM, Tohen M, Stoll AL, Faedda GL, Goodwin DC. Comorbidity in mania at first hospitalization. Am J Psychiatry. 1992;149(4):554-556.

76. Nijjar R, Ellenbogen MA, Hodgins S. Personality, coping, risky behavior, and mental disorders in the offspring of parents with bipolar disorder: A comprehensive psychosocial assessment. Journal of affective disorders. 2014;166:315-23.

77. Swann AC. The strong relationship between bipolar and substance-use disorder. Annals of the New York Academy of Sciences. 2010;1187(1):276-293.

78. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. Science & Practice Perspectives. 2005;3(1):13-21.

79. Henquet C, Krabbendam L, de Graaf R, ten Have M, van Os J. Cannabis use and expression of mania in the general population. Journal of Affective Disorders. 2006;95(1):103-110.

80. Salloum IM, Thase ME. Impact of substance abuse on the course and treatment of bipolar disorder. Bipolar disorders. 2000;2(3p2):269-280.

81. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. American journal of Psychiatry. 1985;142(11):1259-1264.

82. Khantzian EJ. Understanding addictive vulnerability: an evolving psychodynamic perspective. Neuropsychoanalysis. 2003;5(1):5-21.

83. Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. Development and psychopathology. 2006;18(04):1181-1211.

84. Post RM, Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. The British Journal of Psychiatry. 2013;202(3):172-176.

85. Duffy A, Horrocks J, Milin R, Doucette S, Persson G, Grof P. Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high-risk study. Journal of affective disorders. 2012;142(1):57-64.

86. Salloum I. The Clinical Challenge of Comorbid Bipolar Disorder and Substance Use Disorder. Psychiatric Times. 2006;23(9):30.

87. McNamara RK, Jandacek R, Tso P, Blom TJ, Welge JA, Strawn JR, Adler CM, Strakowski SM, DelBello MP. Adolescents with or at ultra-high risk for bipolar disorder exhibit erythrocyte docosahexaenoic acid and eicosapentaenoic acid deficits:

a candidate prodromal risk biomarker. Early intervention in psychiatry. 2015;10(3):203-211.

88. Levenson JC, Axelson DA, Merranko J, Angulo M, Goldstein TR, Goldstein BI, Brent DA, Diler R, Hickey MB, Monk K, Sakolsky D. Differences in sleep disturbances among offspring of parents with and without bipolar disorder: association with conversion to bipolar disorder. Bipolar disorders. 2015;17(8):836-848.

89. Park MH, Sanders E, Howe M, Singh M, Hallmayer J, Kim E, Chang K. Association of Anxiety Symptoms in Offspring of Bipolar Parents with Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR) Genotype. Journal of child and adolescent psychopharmacology. 2015;25(6):458-466.

Table Legends

Table 1 (p. 36-38) provides details on the characteristics of the included studies, grouped into cohorts. The characteristics provided within the table include: cohort name, first author name, citation, year of publication, country, parental characteristics (N, Gender), offspring characteristics (N, Gender, Mean Age), assessment characteristics (DSM measure, assessment tool for parents and for offspring) and if any, follow-up in years and type of control group.

Table 2 (p. 39) presents the heuristic framework used in the review to present results for estimated psychiatric risk in offspring of parents with bipolar disorder (OPBD). The broader categories of psychiatric disorders used are mapped with the specific disorders assessed in at least one of the included papers.

Table 3 (40-44) presents the results of the included studies on the psychiatric risk of OPBD. Findings are placed on a continuum of 5 different developmental stages based on the mean age of the cohort (early childhood 0-6 y.o., middle childhood 6-12 y.o., adolescence 12-18 y.o., early adulthood 18-23 y.o., adulthood >23 y.o.). Risk is separately reported for any Axis I Disorders, Mood and Non-Mood Disorders.

Table 4 (45-47) displays evidence on the sequential onset of mood and non-mood disorders in relation to the onset of mania/hypomania; i.e. clinical staging of bipolar disorder (BD). Associations between a disorder at a certain developmental stage and later onset of BD are highlighted using bold typeset.

Table 5 (48-50) shows the quality assessment results of each study per AHRQ (Agency for Healthcare Research and Quality checklist) item and the total score.

Table 1: Cohort Characteristics

Cohort Author	Country Year/ Citation	Parental Characteristics		Offspring Characteristics			Assessment Characteristics			Follow-up (Years)
		N	Gender (%)	N	Gender (%)	Mean Age (SD)	Measure	Parents	Offspring	
Pittsburgh (BIOS)	**USA**						DSM-IV	SCID, K-SADS-PL	K-SADS-PL	
Birmaher #1*[a]	2009 (50)	233	F=80	388	F=49	11.9 (3.6)				N/A
Axelson*[a]	2015 (23)	236	F=81	391	F=49	T1: 11.9 (3.7) T2: 18.1 (4.8)				6.8
Birmaher #2*[a]	2010 (51)	83	F=90	121	F=52	3.8 (1.3)				N/A
Canada	**Canada**	113	F=52	229	F=60	T1: 16.4 (5.3)	DSM-IV	SADS-L	K-SADS-PL	16
Duffy*[a]	2014 (27)					T2: 22.6 (6.8)			SADS-L	
Dutch	**Netherlands**	T1: 86	T1: F=60	T1:140	T1: F=49	T1: 16.1	DSM-IV	IDCL	K-SADS-	
Reichart	2004 (52)	T2: 82	T2: -	T2:132	T2: F=46	T2: 17.4			PL, SCID-I	1
Hillegers	2005 (53)	T3: 80	T3: F=60	T3:129	T3: F=47	T3: 20.8				5
Mesman	2005 (33)	T4: 70	T4: F=59	T4:108	T4: F=46	T4: 28				12
Amish	**USA**	15	-	115	-	T1: 75% <14	Adapted	Care	Care	16
Egeland*[a]	2012 (30)					T2: 11% <18	DSM-III/ IV	Interview	Interview†	
Lausanne	**Switzerland**	72	F=60	139	F=53	T1: 10.4 (4.3)	DSM-IV	DIGS[d]	K-SADS-E[d]	N/A
Vandeleur*[c]	2012 (20)	81	F=58	145	F=51	T2: 21.1 (5.6)			K-SADS-E[d],	10
Preisig*[c]	2016 (54)								DIGS[d]	
Massachusetts #1	**USA**	88	-	117	F=50	13.6 (5.3)	DSM-IV	SCID	K-SADS-E,	N/A

Henin*[a]	2005 (25)								SCID	
Massachusetts #2 Hirshfeld-Becker*[c]	**USA** 2015 (55)	23	F=55	34	F=62	7.1 (2.6)	DSM-III-R	SCID, K-SADS-E	K-SADS-E	N/A
Massachusetts#3' Freed	**USA** 2015 (56)	109	F=65	188	F=46	13.4 (5.9)	DSM-IV	SCID	K-SADS-E, SCID	N/A
Barcelona #1 Garcia-Amador*[a]	**Spain** 2015 (57)	34	F=55	50	F=42	12.2 (2.9)	DSM-IV-TR	SCID-I	K-SADS-PL	N/A
Barcelona #2 Sanchez-Gistau*[c]	**Spain** 2015 (21)	54	F=57	90	F=98	12.5 (3)	DSM-IV	SCID-I[e]	K-SADS-PL[e]	N/A
Istanbul Erkan*[a]	**Turkey** 2015 (58)	25[2]	F=68	25[2]	F=60	14.2 (1.7)	DSM-IV	SCID-I[f]	K-SADS-PL[f]	N/A
Texas Zappitelli	**USA** 2011 (59)	26	F=83	35	F=43	12.5 (2.9)	DSM-IV-TR	SCID	K-SADS-PL	N/A
Sao Paulo Petresco*[c]	**Brazil** 2009 (60)	43[2]	F=100	43[2]	F=58	11.2 (3.7)	DSM-IV	SCID[g]	K-SADS-PL[g]	N/A
Ohio Singh*[a]	**USA** 2007 (24)	29	F=60	37	F=51	10.2 (2.5)	DSM-IV	SCID-P	WASH-U-KSADS	N/A
Cleveland Findling*[a]	**USA** 2005 (13)	185	F= 58	167[3]	F=41	11 (3.4)	DSM-IV	SADS-LB	K-SADS-E, K-SADS-PL	N/A
Stanford Chang	**USA** 2000 (26)	37	F=84	60	F=42	11.1 (3.5)	DSM-IV	Clinical Interview	WASH-U-KSADS	N/A
Minnesota‡ Radke-Yarrow	**USA** 1992 (31)	26	F=100	22	"More girls than boys"	T1: 2.6 + 6.4 T2: 5.6 + 9.2	DSM-III	SADS-L, RDC	Interview, CAS+CBCL	3
Los Angeles Hammen*[c]	**USA** 1990 (32)	14	F=100	18	F=56	T1:13.6 T2: 16.6	DSM-III	SADS-L	K-SADS	3

Bucharest Grigoroiu-Serbanescu*[a]	**Romania** 1989 (34)	47	F=60	72	F=53	12.9 (2.3)	DSM-III	Clinical Interview	K-SADS-E	N/A
Rockville Zahn-Waxler*[a]	**USA** 1988 (61)	7[2]	F=57	7[2]	F=0	T1: 0-2 T2: 5-6	DSM-III	SADS-L	CAS	4
Illinois Klein*[b]	**USA** 1985 (62)	24	F=54	37	F=49	17.9 (1.9)	DSM-III	SADS, RDC	SADS-L, RDC	N/A

Notes: All percentages are rounded; †Adapted version of WASH-U-KSADS; ‡Some of the demographic information derive from Radke-Yarrow et al., 1998 (63); *Studies with control group; [a]Control group of healthy parents; [b]Control group of non-healthy parents; [c]Control groups of both healthy and non-healthy parents; [d]French version; [e]Spanish version; [f]Turkish version; [g] Brazilian version; ' Sample is consisted from Henin et al., 2005 (25) sample and a subsequent sample; [2]Each offspring comes from an independent family; [3]Clinical population; CAS: Child Assessment Schedule; CBCL: Child Behaviour Checklist; DIGS: Diagnostic Interview for Genetic Studies; DSM: Diagnostic and Statistical Manual of Mental Disorders; F: Female; IDCL: International Diagnostic Checklists; K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological version; N/A: Not Applicable: Cross-Sectional Study design; SADS: Schedule for Affective Disorders and Schizophrenia; K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version; SADS-L: Schedule for Affective Disorders and Schizophrenia, Lifetime version; ; RDC: Research Diagnostic Criteria; SD: Standard Deviation; SADS-LB: Schedule for Affective Disorders and Schizophrenia, Lifetime version for Bipolar Disorder; SCID: Structured Clinical Interview for DSM; SD: Standard Deviation; WASH-U-KSADS: Washington University Schedule for Affective Disorders and Schizophrenia for School-Age Children; T1: Time 1; T2: Time 2; T3: Time 3; T4: Time 4

Table 2. Categories of disorders measured in included papers mapped with specific disorders.

Bipolar Spectrum Disorders	Unipolar Spectrum Disorders	Anxiety Disorders	Behaviour Disorders	Other Disorders
Bipolar type I disorder (BD-I)	***Major:***	Generalized anxiety disorder (GAD)	Oppositional Defiant Disorder (ODD)	Substance use disorder (SUD)
Bipolar type II disorder (BD-II)	Major depressive disorder (MDD)	Separation anxiety disorder (SAD)	Conduct Disorder (CD)	Sleep disorder (SLD)
Bipolar disorder not otherwise specified (BDNOS)	***Minor:***	Obsessive compulsive disorder (OCD)	Attention Deficit Hyperactivity Disorder (ADHD)	
Cyclothymia (Cycl.)	Dysthymia	Overanxious disorder		
	Adjustment disorder with depressed mood	Simple/Specific phobias (SP)		
	Depression not otherwise specified	Social phobia (SOP)		
		Panic disorder (PD)		
		Post-traumatic stress disorder (PTSD)		

Table 3: Risk of Psychopathology in OPBD

Cohort *Timing of Diagnosis* Citation	Year of publi-cation	Mean Age/ Age Range	%age of Sample with Axis I Diagnoses	Mood Disorders		Non-Mood Disorders			
				Bipolar Spectrum Disorders	Unipolar Spectrum Disorders	Anxiety Disorders	Behaviour Disorders		Other Disorders
							ADHD	ODD/CD	
Early Childhood									
Minnesota *Lifetime (31)*	1992	2.4	-	-	0%	9%	-	15%	-
Pittsburgh *Lifetime (51)*	2010	3.8	26%*	2% NS BD- NOS	1% NS	11% NS	16%*	ODD: 12% (p<0.07) CD: 2% NS	SLD: 3 NS
Los Angeles *CI (32)*	1990	0-4	1% [a]	-	Major: 0%	-	-	-	-
Rockville *Lifetime (61)*	1988	5-6	86%	-	43%	14%-43%	-	CD: 43%	-
Minnesota *Lifetime (31)*	1992	5.6	-	-	24% †	9%	-	24% †	-
Lausanne *CI (20)*	2012	6	-	21% (any mood disorder)		29%	-	-	-
Middle Childhood									
Minnesota *Lifetime (31)*	1992	6.4	-	-	17%	11%	-	28%	-
Massachusetts #2 *Lifetime (55)*	2006	7.1	-	9%* BD-I: 6%*	Major: 9% NS Minor: 3% NS	44%*, **	24%**	ODD: 9% NS CD: 3% NS	-

Massachusetts #1	2005	8	-	9 %*	23%*	3%-18%*	22% *	ODD: 19% NS	SUD: 0%
CI (25)				BD-I				CD: 2% NS	NS
Los Angeles	1990	5-9	32% [a]	-	Major: 6%	-	-	-	-
CI (32)									
Minnesota	1992	9.2	-	-	44% †	44% †	-	28%	-
Lifetime (31)									
Ohio	2007	10.2	78%*	38%*	Major: 14% NS	32% NS	31%*	22%*	-
Lifetime (24)				BD-I: 16% NS	Minor: 14% NS				
Cleveland	2005	11	89%	74%*	8% NS	1% NS	4% NS	0% NS	SUD: 0%
Lifetime (13)				BD-I: 37%					
Stanford	2000	11.1	55%	15%	15%	8%	28%	ODD: 10%	-
Lifetime (26)				BD or Cycl.					
Sao Paulo	2009	11.2	63%*.**	2% NS	5% NS	44%*.**	12%***	ODD: 7%***	-
Lifetime (60)								CD: 7%***	
Lausanne	2012	11.8	62%*	4% NS	31%*	43%*	8% NS	8% NS	SUD: 9%
Lifetime (20)				BD-I or II: 2% NS	Major: 19%*				NS
Pittsburgh	2009	11.9	52%*	11%*	Major: 9%*	26%*	25% *	ODD: 17% *	SUD: 4%
Lifetime (50)				BD-I: 2%*	Minor: 2% NS			CD: 4% NS	NS
Adolescence									
Massachusetts #1	2005	12	-	12%*	34%*	4% - 21%*	22%*	ODD: 28% NS	SUD: 3% NS
CI (25)								CD: 6% NS	
Lausanne	2012	12	-	28%* (any mood disorder)		46%*	-	-	-
CI (20)									
Pittsburgh	2009	12	-	12%	Major: 9%	-	-	-	-
CI (50)									

Barcelona #1 *Lifetime (57)*	2013	12.2	50% *	4% NS	Major: 6% NS	14% NS	18% NS	ODD: 12% NS	SUD: 2% NS
Barcelona #2 *Lifetime (21)*	2015	12.5	37% *	0% NS Hypomania/Mania	Major: 7%* Minor: 9% NS	12% NS	18%*	3% NS	-
Texas Lifetime (59)	2011	12.5	71%	9% BD-I: 6%	Major: 20% Minor: 3%	3% - 14%	40%	ODD: 14% CD: 3%	-
Bucharest *Current (34)*	1989	12.9	61 %*	1% NS	8%*	12%*	21%*	ODD: 3% NS CD: 11% NS	-
Massachusetts #3 Lifetime (56)	2015	13.4	-	21%	25%	46%	27%	34%	-
Istanbul *Lifetime (58)*	2015	14.2	48%*	4% NS	16% NS	12% NS	8% NS	CD: 8% NS	SUD: 8% NS
Los Angeles *CI (32)*	1990	10-14	52%[a]	-	Major: 20%	-	-	-	-
Los Angeles *Lifetime (32)*	1990	16.6	72%	0%	Major: 22% Minor: 39%	11% - 17%	6%	22%	SUD: 11%
Dutch *Lifetime (52)*	2004	17.4	49%	5% BD-I or BD-II: 4%	Major: 8% Minor: 22%	11%	5%	7%	SUD: 9%
Illinois *Lifetime (62)*	1985	17.9	43% **	27%** Cycl.: 24%**	Major: 3% NS Minor: 8% NS	5% NS	-	11% NS	SUD:19% NS
Amish *Lifetime (30)*	2012	"Adole-scents"	-	7%* BD-I	-	-	-	-	-
					Early Adulthood				
Pittsburgh *CI (50)*	2009	18	-	18%	Major: 24%	-	-	-	-
Pittsburgh	2015	18.1	74%*	19%*	Major: 19%*	40%*	31%*	ODD:25%*	SUD:20%*

Lifetime (23)				BD-I: 4%*	Minor: 10%*			CD:10%	
Los Angeles	1990	15-19	76%[a]	-	Major: 33%	-	-	-	-
CI (32)									
Massachusetts #1	2005	18	-	33%*	51% *	10% -	22% *	ODD:33% [NS]	SUD:14%[NS]
CI (25)						21%*		CD:11% [NS]	
Lausanne	2012	18	-	64%* (Any mood disorder)		48% *	-	-	-
CI (20)									
Dutch	2005	21	59%	10%	Major: 10%	21%	5%	7%	SUD:16%
Lifetime (53)				BD-I or BD-II	Minor: 24%				
Lausanne	2016	21.1	-	17% **	Major: 37% [NS]	44% [NS]	17% [NS]	ODD:15% [NS]	SUD:28%[NS]
Lifetime (54)				BD-I or BD-II	Minor: 9% [NS]			CD:12% [NS]	
Canada	2014	22.6	-	22%*	Major: 32%*	23% *	11% [NS] ‡	2% [NS]	SUD: 30%*
CI (27)					Minor: 30% [NS]				SLD: 21%*
Adulthood									
Dutch	2013	28	72%	13%	Major: 17%	25%	5%	7%	SUD: 23%
Lifetime (33)				BD-I or BD-II: 11%	Minor: 28%				

Notes: All percentages are rounded; Bipolar Spectrum Disorders include: Bipolar type I disorder (BD-I), Bipolar type II disorder (BD-II), Bipolar disorder not otherwise specified (BD-NOS), Cyclothymia (Cycl.); Unipolar Spectrum Disorders include: Major: Major depressive disorder; Minor: Dysthymia, Adjustment disorder with depressed mood, Depression not otherwise specified; Anxiety Disorders include: Generalized anxiety disorder, Separation anxiety disorder, Obsessive compulsive disorder, Overanxious disorder, Post-traumatic stress disorder, Social phobia, Panic Disorder, Simple/Specific phobias; ADHD: Attention Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; CD: Conduct Disorder; SLD: Sleep Disorder; SUD: Substance Use Disorder; CI: Cumulative Incidence (Confidence Interval 95%); *Significantly different compared to non-psychiatric control group (at least $p < 0.05$); **Significantly different to psychiatric control group (at least $p < 0.05$); *** Significantly different compared to both control groups as a whole (at least $p < 0.05$); NS: Non significant; -: Not measured; †Significantly changed over time; ‡ Prevalence rate includes ADHD, learning disorder, Cluster A traits [a] cumulative probability of major definite diagnoses (excluding minor depression and non-diagnosable symptoms)

Table 4: Disorder Onset and Clinical Staging Findings

Cohort Year[a] Citation	Study Design Country Age Range/ Follow-up	Prior to Mania/Hypomania Non-Mood Disorders (SD)	 Mood Disorders (SD)	Mania/Hypomania (SD)	Subsequent to Mania/Hypomania Non-Mood Disorders (SD)	 Mood Disorders (SD)
Massachusetts #1* 2005 (25)	Cross-Sectional USA 4-18	5: ADHD 5.9-6.7: AD 7.6: ODD 9.9: CD	9.3: MDD	10: Mania	-	-
Massachusetts #3 2015 (56)	Cross-Sectional USA 4-33	3.7 (2): ADHD 4.6 (2.8): AD 7.4 (3.7): DBD	8.9 (4.2): Depression	9.3 (5): Mania (7.6 (3.9): BD)	-	-
Stanford 2000 (26)	Cross-Sectional USA 6-18	-	-	10.9 (3.2): BD	11.3 (3.3): ADHD	12.3 (3.5): Depression
Amish 2012 (30)	Longitudinal USA (Amish) Birth-30s	0-6**: Crying, hyper-alert, anxiety/worry, somatic complaints** 7-12: **Increased anxiety type symptoms, decreased sleep and energy, mood lability, fearfulness, role impairment**		17 (5.9) [b]: Mania	-	
Canada ** 2014	Longitudinal Canada	5 (20): ND 9.4 (10): DBD	16 (4.1)	20 (5) [b]: Mania/Hypomania	-	-

(27)	7-30	**9.8 (4.2): AD** 9.9: SLD 17.5 (3.1): SUD 18.4: Psychotic disorder	(for 84% in the depressive polarity)			
Dutch (Mesman) 2013 (33)	Longitudinal Netherlands 12-33	17.1 (8): comorbid AD (67% prior) 17.7 (1.5): comorbid SUD (in every case prior)	14.6 (4.7) (in every case prior, for 88% in the depressive polarity)	17.3: Hypomania 20.2 [c]: Mania	-	-
Pittsburgh (Axelson) 2015 (23)	Longitudinal USA 6-25	ADHD (42% prior) AD (53% prior) **DBD (48% prior)**	12.5 (4.6): Depressive episode (70% prior) **13.7 (4): MDD (56% prior)** **Subthreshold (hypo) manic episode (36% prior)**	13.4 (3.8) [d]: Mania/Hypomania (12.1 (4): BD)	SUD (94% subsequent)	-

Notes: All percentages are rounded; Mood disorders do not include bipolar disorder, manic or hypomanic episode; Text in bold: Predictive association to first (hypo)manic episode; AD: Anxiety Disorders; ADHD: Attention deficit hyperactivity disorder; BD: Bipolar disorder; CD: Conduct Disorder; DBD: Disruptive Behavior Disorders (includes ODD/CD); MDD: Major Depressive disorder; ND: Neurodevelopmental disorders, which include ADHD, learning disorder and Cluster A traits; ODD: Oppositional Defiant Disorder; SD: Standard Deviation; SLD: Sleep disorder; SUD: Substance Use Disorders; [a]In case of longitudinally followed cohorts, data from the most recent follow-up are reported; [b]None of the participants had pre-pubertal manic or hypomanic episode; [c]29% pre-pubertal onset of depressive episode; [d]86% pre-pubertal onset of manic episode; * Detailed age of onset derive from Massachusetts #2 paper (55); ** In cases of inconsistency in tables and in-text reporting of the onset ages, the in-text information was included in this table

Table 5: Quality Assessment Results

Author Year Citation	Unbiased selection of cohort	Selection minimizes baseline	Sample size calculated	Adequate description of the cohort	Validated method for ascertaining high	Validated method for ascertaining	Outcome assessment blind to exposure	Adequate follow-up period	Report missing data/ drop-out	Analysis control for confounding	Analytic Methods	Appropriate	Total Score	Percentage Score
Birmaher 2009 (50)	Y	Y	N	Y	Y	Y	Y	N/A	Y	Y	Y		**18**	**90%**
Axelson 2015 (23) *	Y	Y	N	Y	Y	Y	Y	Y	P	Y	Y		**19**	**86%**
Birmaher 2010 (51)	Y	Y	N	Y	Y	Y	Y	N/A	Y	Y	Y		**18**	**90%**
Duffy 2014 (27) *	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y		**16**	**73%**
Reichart 2004 (52)	Y	N/A	N	P	Y	Y	N	Y	Y	N	Y		**13**	**65%**
Hillegers 2005 (53)	Y	N/A	N	Y	Y	Y	N	Y	Y	N	Y		**14**	**64%**
Mesman 2013 (33)	Y	N/A	N	Y	Y	Y	N	Y	Y	P	Y		**15**	**75%**
Egeland 2012 (30) *	Y	Y	N	N	P	P	Y	Y	Y	N	Y		**14**	**64%**
Vandeleur 2012 (20) *	Y	P	N	Y	Y	Y	Y	N/A	P	Y	Y		**16**	**80%**

Preisig 2016 (54)	Y	P	Y	Y	Y	Y	Y	Y	N	Y	Y	**19**	**86%**
Henin 2005 (25)	Y	P	N	Y	Y	Y	Y	N/A	N	Y	Y	**15**	**75%**
Hirshfeld-Becker 2006 (55)	Y	N	N	Y	Y	Y	Y	N/A	N	Y	Y	**14**	**70%**
Freed 2015 (56)	Y	N/A	N	Y	Y	Y	N	N/A	Y	Y	Y	**14**	**78%**
Garcia-Amador 2013 (57) *	Y	N	N	Y	Y	Y	N	N/A	N	Y	Y	**12**	**60%**
Sanchez-Gistau 2015 (21)	Y	N	N	Y	Y	Y	Y	N/A	Y	Y	Y	**16**	**80%**
Erkan 2015 (58) *	Y	N	N	Y	Y	Y	N	N/A	N	Y	Y	**12**	**60%**
Zappitelli 2011 (59)	Y	N/A	N	Y	Y	Y	N	N/A	N	P	P	**10**	**56%**
Petresco 2009 (60) *	Y	N	N	Y	Y	Y	Y	N/A	Y	Y	Y	**16**	**80%**
Singh 2007 (24) *	Y	Y	N	Y	Y	Y	Y	N/A	N	Y	Y	**16**	**80%**
Findling 2006 (13) *	P	N	N	Y	Y	Y	Y	N/A	N	Y	Y	**13**	**65%**
Chang 2000 (26)	Y	N/A	N	Y	P	Y	N	N/A	N	Y	Y	**11**	**61%**
Radke-Yarrow	Y	P	N	P	Y	P	P	Y	Y	Y	Y	**16**	**73%**

1992 (31)													
Hammen	Y	N	N	Y	Y	P	P	Y	P	Y	Y	**15**	**68%**
1990 (32)													
Grigoroiu-	Y	Y	N	Y	P	Y	Y	N/A	Y	Y	Y	**17**	**85%**
Serbanescu													
1989 (34) *													
Zahn-Waxler	N	Y	N	Y	Y	Y	Y	Y	Y	N	P	**15**	**68%**
1988 (61)													
Klein	Y	N	N	Y	Y	Y	Y	N/A	N	Y	P	**13**	**65%**
1985 (62)													

Notes: Y= Yes; N=No; P=Partially, N/A: This question was not applicable for the study; *Independently rated by a second researcher